Critical Care

REVIEW

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Impact of oxygen and carbon dioxide levels on mortality in moderate to severe traumatic brain injury: a systematic review and meta-analysis

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Abstract

Background Traumatic brain injury (TBI) remains a leading cause of morbidity and mortality worldwide. Secondary brain insults related to oxygenation and ventilation may affect outcomes in this high-risk population. The aim of this study was to perform a comprehensive review examining the relationship between oxygen and carbon dioxide thresholds and mortality to guide clinical care.

Methods Eleven databases, including: MEDLINE, MEDLINE In-Process, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, CINAHL, APA PsycINFO, Web of Science, Biosys, Scopus, and the Global Index Medicus, were systematically searched from inception to October 23, 2024. Included studies reported on adults (≥18 years) with moderate to severe TBI (msTBI) (Glasgow Coma Scale <13 or Head Abbreviated Injury Scale ≥3) and exposure to hypoxia, hypocapnia, or hypercapnia, with mortality or vegetative state data reported within 6 months. Vegetative state data was not reported, so all analyses were based on mortality. Pediatric or mild TBI studies, stroke-focused studies, and studies without mortality outcomes were excluded. The data were screened via Covidence software with multiple reviewers. No language or regional restrictions were applied. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Quality was assessed via the Newcastle-Ottawa Scale (NOS) for Cohort Studies, and certainty of evidence was rated using GRADE. Four authors independently extracted data with verification by a second reviewer. The primary outcome was measured using odds ratios (ORs) with 95% confidence intervals (CIs), calculated separately for crude and adjusted effect estimates.

Results Twenty-one cohort studies with 41,980 patients were included. Hypoxia and hypocapnia were significantly associated with increased mortality (aOR, 1.39; 95% CI 1.11–1.75; p =.005; aOR, 1.64; 95% CI 1.25–2.15; p <.001). Hypercapnia was not significantly associated with mortality (aOR, 1.74; 95% CI 0.91–3.32; p =.09).

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Conclusions In adults with msTBI, hypoxia and hypocapnia were independently associated with increased mortality, underscoring the importance of prompt recognition and targeted management of these secondary injuries. The role of hypercapnia remains unclear, warranting further investigation.

Keywords Hypoxia, Hypocapnia, Hypercapnia, TBI, Meta-analysis

Introduction

Traumatic brain injury (TBI) remains a leading cause of long-term disability, morbidity, and mortality worldwide, with approximately 13.1 million cases of msTBI occurring annually [1]. This preventable condition imposes a substantial societal and economic burden through acute care, long-term rehabilitation, and ongoing neurological support [2]. While the initial mechanical insult or primary injury is irreversible, [3] the development of secondary brain injury, caused by impaired cerebral perfusion, systemic hypoxia, carbon dioxide (CO_2) imbalance, and elevated intracranial pressure (ICP), presents a crucial therapeutic window for intervention [4].

Previous observational studies have linked hypoxia and both hypo- and hypercapnia to increased mortality in patients with msTBI, highlighting the importance of early recognition and correction of these physiological disturbances to minimize further neuronal damage and optimize outcomes [5–7]. In alignment with these findings, the 4th edition of the Brain Trauma Foundation (BTF) guidelines for sTBI management recommended avoiding profound hypocapnia (arterial partial pressure of CO_2 [$PaCO_2$] < 25 mmHg) [8]. However, these recommendations lack clearly defined thresholds for systemic oxygenation and hypercapnia, highlighting gaps in the literature. As the global burden of TBI rises, [9] research on oxygenation and ventilation disturbances has increased, but systematic reviews quantifying their links to mortality remain limited.

To address this need, we conducted a meta-analysis to examine the relationship between systemic oxygen (O_2) and CO_2 thresholds and mortality in adults with msTBI, aiming to provide a clearer understanding of their impact on patient prognosis. By integrating the available evidence, this review seeks to offer clinically relevant insights that may guide treatment strategies and contribute to improved survival and functional outcomes in this high-risk population.

Methods

This systematic review and meta-analysis was reported following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [11] (Additional file 1: Table S1 and Table S2). The study protocol was registered in PROSPERO on October 9, 2024 (CRD42024595641).

Search strategy

An information specialist (ME) developed a comprehensive search strategy. The following databases were searched from inception to October 23, 2024: MEDLINE, MEDLINE ePubs Ahead of Print and In-Process Citations, Embase Classic+Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and APA PsycINFO, all via the Ovid platform; CINAHL (Cumulative Index to Nursing & Allied Health Literature, Ebsco), the Web of Science (Clarivate Analytics), Biosys Previews (Clarivate Analytics), Scopus (Elsevier), and the Global Index Medicus (WHO). The database search results and MEDLINE search strategy are included in Additional file 1: Table S3.

Eligibility criteria

The inclusion criteria were primary research articles that investigated the associations between hypoxia, hypocapnia, or hypercapnia and mortality in adult patients ($\geq$ 18 years) with msTBI. Hypoxia, hypocapnia, and hypercapnia were defined using the different thresholds specified by the individual studies. The most common thresholds were SpO_2 < 90% for hypoxia and $PaCO_2$ < 30 mmHg for hypocapnia, no common threshold for hypercapnia was identified. Studies assessing these insults in prehospital and/or in-hospital settings were included. msTBI was defined as a Glasgow Coma Scale (GCS) score of 12 or lower, or a Head Abbreviated Injury Scale (AIS) score of 3 or greater. These definitions are outlined in Additional file 1. Studies with both isolated and polytrauma were included. Eligible study designs included randomized controlled trials (RCTs), quasi-randomized, prospective cohort, retrospective (case–control or cohort), longitudinal, cross-sectional, and observational studies. The primary outcome was a composite Glasgow Outcome Scale-Extended (GOS-E) score of 1 and/or 2, defined as death or vegetative state within 6 months. No included studies reported vegetative state, so all analyses were based solely on mortality data. Mortality was measured in-hospital for 15 of the 21 included studies (Additional File 1: Tables S4-6). Studies published in any language were eligible for inclusion.

Articles were excluded if they: (1) included patients < 18 years of age, unless a subgroup analysis was performed for adult patients; (2) included patients with mild TBI, unless a subgroup analysis was performed for patients with msTBI; (3) included patients with a primary admission diagnosis of stroke; (4) reported hyperoxia

or cerebral hypoxia as the only exposure; (5) reported a composite outcome in which mortality data could not be extracted; (6) did not report mortality outcomes within a maximum 6 month follow-up period; (7) were abstracts; or (8) were secondary research articles such as post-hoc analyses, case reports, or reviews.

For studies eligible for screening where the full text could not be located, both the first author and the corresponding author were contacted via email to request access.

Data extraction

Title and abstract screening and subsequent full-text screening were carried out via Covidence software. Four independent reviewers performed the initial title and abstract screening, full-text screening, and data extraction (TAJ, MCSA, AR, AAR). Any conflicts that arose during screening were resolved through consensus or by consulting the principal investigator (TC). All extracted data were reviewed by a second author to ensure accuracy.

Outcomes

Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were the principal measures of effect for mortality outcome data. The crude ORs and adjusted ORs of each exposure-outcome pair were analyzed separately to account for heterogeneity across the exposures. When a study reported only raw mortality data for patients in the affected and unaffected groups, the crude OR was calculated manually. Forest plots were used to visualize the OR and effect size of the individual studies and the overall OR and effect size within each exposure-outcome pair. Additional forest plots were created to visualize the results of the subgroup analyses by TBI severity and O_2 or CO_2 parameters within each exposure-outcome pair.

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) for Cohort Studies was used to rate the quality of the included studies [12]. Additionally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to rate the quality of evidence [13]. Unadjusted odds ratios (crude ORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated.

Statistical analysis

The meta-analysis was conducted in Stata 18. Given that the search was not restricted by language or publication year, some heterogeneity was expected to be present across the studies. To account for this and enhance the generalisability of the results, a random-effects meta-regression model was chosen *a priori*. 95% prediction intervals were used for each exposure-outcome group to determine the expected effect size of future studies. For the analysis, study-level adjusted estimates were used.

Galbraith plots were used to visually display heterogeneity and identify outlier studies. Heterogeneity was also quantified via I^2. Leave-one-out analyses were performed for each exposure-outcome group to identify individual studies that disproportionately affected the overall results. Publication bias was quantified via Begg's and Egger's tests and displayed visually with contour-enhanced funnel plots. Trim-and-fill analysis was used to adjust for this potential bias. The statistical significance level was set at $p \leq 0.05$.

Results

The systematic search yielded 14,311 studies after removing 9,577 duplicates. A total of 328 full-texts were sought for retrieval, and 12 could not be obtained despite consulting academic libraries and multiple attempts to contact the first and/or corresponding authors. Ultimately, 316 full-texts were assessed for eligibility, and 21 studies [4, 5, 7, 14-31] met the inclusion criteria for the final analysis (Fig. 1). A summary of the study characteristics is provided in Table 1. Further study characteristics and patient demographic data are available in Additional file 1: Tables S4-6. A total of 41,980 adult patients across studies published from 1973-2024 were included. All included articles were cohort studies published in English. They were all scored on the NOS as good or fair, with a median rating of 8 (range 6-9) [12] (Additional file 1: Table S7). GRADE revealed low- to moderate-quality evidence for the exposure-outcome pairs (Additional file 1: Table S8). Seventeen studies assessed hypoxia, hypocapnia, and hypercapnia in-hospital, 2 measured pre-hospital, and 2 measured them in both settings.

A total of 37,978 patients were included across the 12 hypoxia studies. Six studies assessed hypoxia using partial pressure of arterial O_2 (PaO_2) and 6 studies used peripheral capillary O_2 saturation (SpO_2). The most common threshold for hypoxia was SpO_2 < 90% (4 studies; Additional file 1: Table S4). Figure 2a depicts a forest plot of the crude ORs calculated for hypoxia and mortality among these studies. Hypoxia nearly tripled the odds of mortality (crude OR, 2.94; 95% CI 1.34−6.45; p = 0.007). As shown in Fig. 3a, the associations persisted in the adjusted models, which accounted for age, sex, hypotension, mechanism of injury, and Injury Severity Score (ISS), (aOR, 1.39; 95% CI 1.11−1.75; p = 0.005). Subgroup analyses of O_2 or CO_2 parameter and TBI severity (mixed versus severe) for the various exposure-outcome pairs are shown in Additional file 1: Fig. S1-5. Neither SpO_2 nor PaO_2 were significantly associated with mortality after adjustment (aOR, 1.82; 95% CI 0.97−3.40; p =

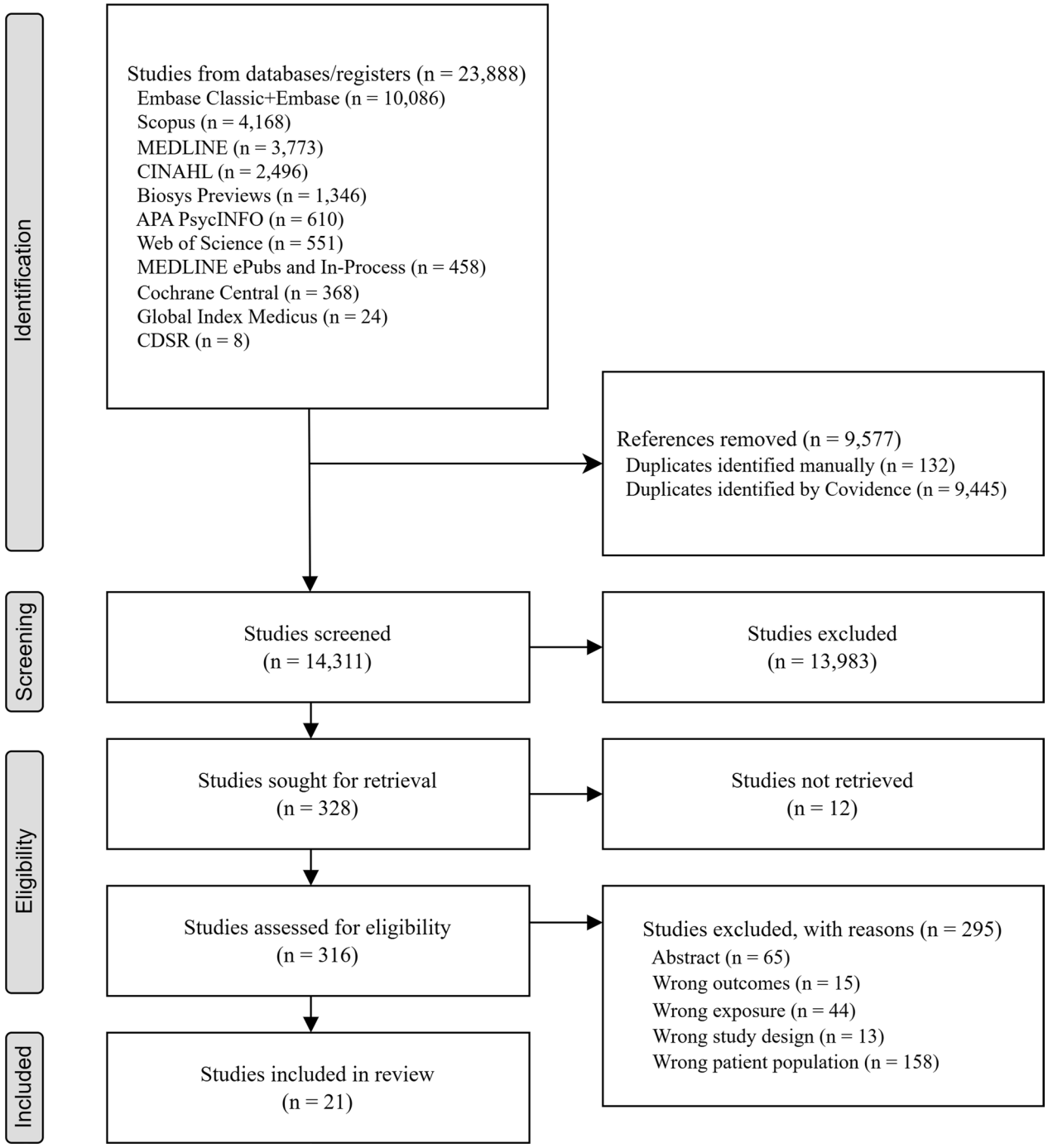
Identification
Studies from databases/registers (n = 23,888)
Embase Classic+Embase (n = 10,086)
Scopus (n = 4,168)
MEDLINE (n = 3,773)
CINAHL (n = 2,496)
Biosys Previews (n = 1,346)
APA PsycINFO (n = 610)
Web of Science (n = 551)
MEDLINE ePubs and In-Process (n = 458)
Cochrane Central (n = 368)
Global Index Medicus (n = 24)
CDSR (n = 8)
References removed (n = 9,577)
Duplicates identified manually (n = 132)
Duplicates identified by Covidence (n = 9,445)
Screening
Studies screened (n = 14,311)
Studies excluded (n = 13,983)
Eligibility
Studies sought for retrieval (n = 328)
Studies not retrieved (n = 12)
Studies assessed for eligibility (n = 316)
Studies excluded, with reasons (n = 295)
Abstract (n = 65)
Wrong outcomes (n = 15)
Wrong exposure (n = 44)
Wrong study design (n = 13)
Wrong patient population (n = 158)
Included
Studies included in review (n = 21)

Fig. 1 PRISMA flow diagram for study selection

0.06; aOR, 1.29; 95% CI 1.00−1.68; p = 0.05; Additional file 1: Fig. S2).

The 11 hypocapnia studies included 13,256 patients. Eight studies assessed hypocapnia using $PaCO_2$ and 3 studies used end-tidal CO_2 ($EtCO_2$). The most common threshold for hypocapnia was $PaCO_2$ < 30 mmHg (Additional file 1: Table S5). Hypocapnia was strongly correlated with mortality both before (crude OR, 1.41; 95% CI 1.04−1.91; p = 0.03) and after adjustment for key variables: age, sex, hypotension, and mechanism of injury (aOR, 1.64; 95% CI 1.25−2.15; p < 0.001). Subgroup analysis revealed that this relationship remained significant when hypocapnia was measured by $EtCO_2$, but not by $PaCO_2$ (crude OR, 1.90; 95% CI 1.55−2.33; p = 0.00; crude OR, 1.23; 95% CI 0.88−1.71; p = 0.22; Additional file 1: Fig. S3).

Table 1 Study characteristics of articles evaluating oxygen and carbon dioxide thresholds in TBI

Study	No. of Patients	TBI Severity Criteria	Threshold(s)	Mortality Timing	Insult Timing
Shen [7]	269	GCS ≤ 8	$SpO_2 < 90$	In-hospital	In-hospital
Vos [16]	79	GCS ≤ 12	$SpO_2 < 90$	At 6 months	In-hospital
O'Connell [19]	281	GCS ≤ 12	$SpO_2 < 90$	Within 24 h	In-hospital
Pakkanen [18]	651	GCS ≤ 8	$SpO_2 \leq 90$	Within 6 months	Prehospital
Davis [30]	236	GCS ≤ 8	$SpO_2 < 90$, $SpO_2 < 70$	In-hospital	In-hospital
Robba [27]	673	GCS ≤ 12	$PaO_2 < 80$	In-hospital	In-hospital
O Briain [29]	17354	GCS ≤ 12, GCS ≤ 8	$PaO_2 < 60$	In-hospital	In-hospital
Asher [21]	193	GCS ≤ 8	$PaO_2 < 60$	In-hospital	In-hospital
Davis [23]	3420	Head AIS ≥ 3	$PaO_2 < 110$	In-hospital	In-hospital
Davis [24]	9018	Head AIS ≥ 3	$PaO_2 < 90$	In-hospital	In-hospital
Para [26]	70	GCS ≤ 8	$PaO_2 \leq 90$	In-hospital	In-hospital
Gao [28]	5734	GCS ≤ 8	$SpO_2 < 95$	In-hospital	In-hospital
Esnault [15]	110	GCS <= 8	$PaCO_2 < 35$	In-hospital	In-hospital
Bossers [5]	1776	GCS ≤ 8	$EtCO_2 < 35$	At 30 days	Prehospital
Lal [31]	40	GCS ≤ 12*	$PaCO_2 \leq 35$	In-hospital	Mixed
Caulfield [4]	100	GCS ≤ 8	$EtCO_2 < 30$	In-hospital	Mixed
Davis [22]	890	Head AIS ≥ 3	$PaCO_2 < 30$, $PaCO_2 < 25$, $PaCO_2 < 20$	In-hospital	In-hospital
Davis [17]	293	GCS ≤ 8	$PaCO_2 < 25$	Within 24 h	In-hospital
Robba [20]	715	GCS ≤ 12	$PaCO_2 < 32$	In-hospital	In-hospital
Crockard [25]	12	n/a*	$PaCO_2 < 30$	Within 3 months	In-hospital
Lee [14]	66	GCS ≤ 8	$PaCO_2$ 30-35, $PaCO_2 < 30$	In-hospital	In-hospital

GCS = Glasgow Coma Scale, AIS = Abbreviated Injury Scale, SpO_2 = blood oxygen saturation, PaO_2 = arterial partial pressure of oxygen,

$PaCO_2$ = arterial partial pressure of carbon dioxide, $EtCO_2$ = end-tidal carbon dioxide

* = Severe head injury specified, but exact GCS/AIS criteria not listed

12,399 patients were included across the 4 hypercapnia studies. Three studies assessed hypercapnia via $PaCO_2$ and 1 used $EtCO_2$. Each study used a different threshold for hypercapnia (Additional file 1: Table S6). All 4 studies reported pathological rather than permissive hypercapnia. Unadjusted analysis revealed a nonsignificant association between hypercapnia and mortality (crude OR, 1.65; 95% CI 0.64−4.28; p = 0.3). After covariate adjustment for age, sex, mechanism of injury, hypotension, and ISS, the association remained weak (aOR, 1.74; 95% CI 0.91−3.32; p = 0.09). However, the association of hypercapnia with mortality was significant when measured by $PaCO_2$ (aOR, 2.17; 95% CI 1.07−4.37; p = 0.03; Additional file 1: Fig. S5).

There was moderate to high statistical heterogeneity between studies. Galbraith plots for each exposure-outcome pair visually displayed heterogeneity, as shown in Additional file 1: Fig. S6-11 and Table S9. No study was identified as an outlier. There was weak evidence of publication bias (p >0.10, Begg's and Egger's tests; Additional file 1: Fig. S12-15 and Table S10).

Discussion

To our knowledge, this is the most comprehensive and current meta-analysis evaluating the associations between systemic oxygenation and ventilation parameters and mortality in adult patients with msTBI. The results demonstrate significant links between hypoxia and hypocapnia with poor outcomes in this population, reinforcing the importance of early recognition and correction of these secondary brain insults during neurocritical management.

Adjusted analyses showed hypoxia was associated with a 39% increase in mortality. This aligns with a prior prospective cohort study which found prehospital hypoxia to be an independent predictor of mortality in patients of any age with msTBI, increasing odds by 166% [32]. Similarly, a more recent cross-sectional analysis of patients with TBI across all severity levels reported elevated mortality odds of 84% for mild hypoxia and 124% for severe hypoxia. The pathophysiological mechanisms underlying this association involve impaired oxygen delivery, prolonged neuroinflammation, biomarker extravasation, and metabolic stress [33, 34]. Together, these data support the critical role of early airway management and adequate oxygenation strategies aimed at preventing hypoxia in this high-risk population.

Among hypocapnic patients, our analysis identified a 64% increase in the odds of mortality after adjustment for cofounders. A large cohort study involving nearly 15,000 adults with TBI reported that prehospital hypocapnia was associated with an adjusted relative risk of 7.99 (95% CI, 2.47−25.85) for emergency department (ED) mortality, corresponding to a 699% increase in risk [35]. Further

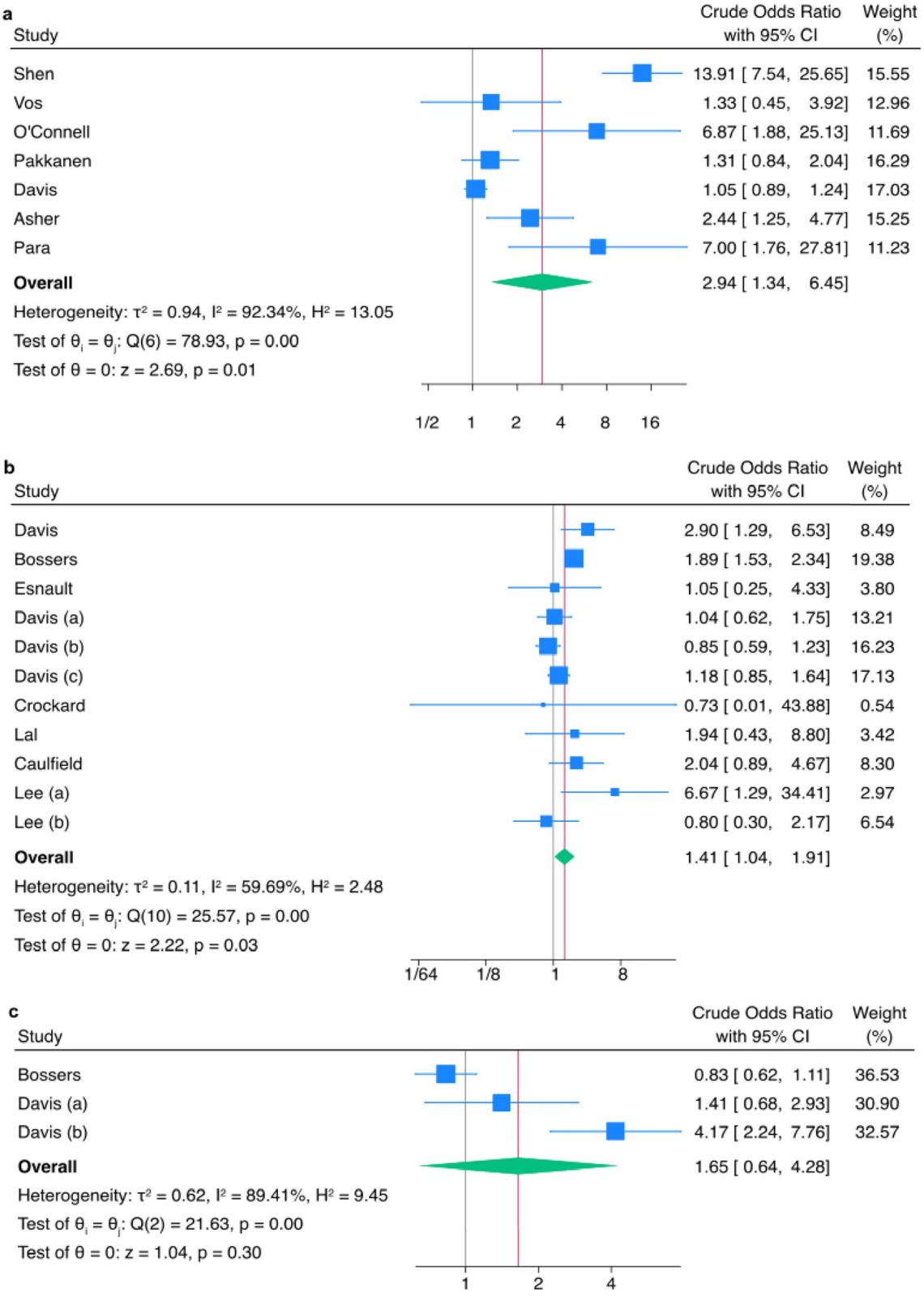

Fig. 2 Forest plots showing random-effects meta-analysis of crude ORs for **a** hypoxia, **b** hypocapnia, and **c** hypercapnia. The vertical red line represents the summary measure; the vertical gray line represents the line of no effect; the diamond represents the overall pooled effect estimate of crude OR

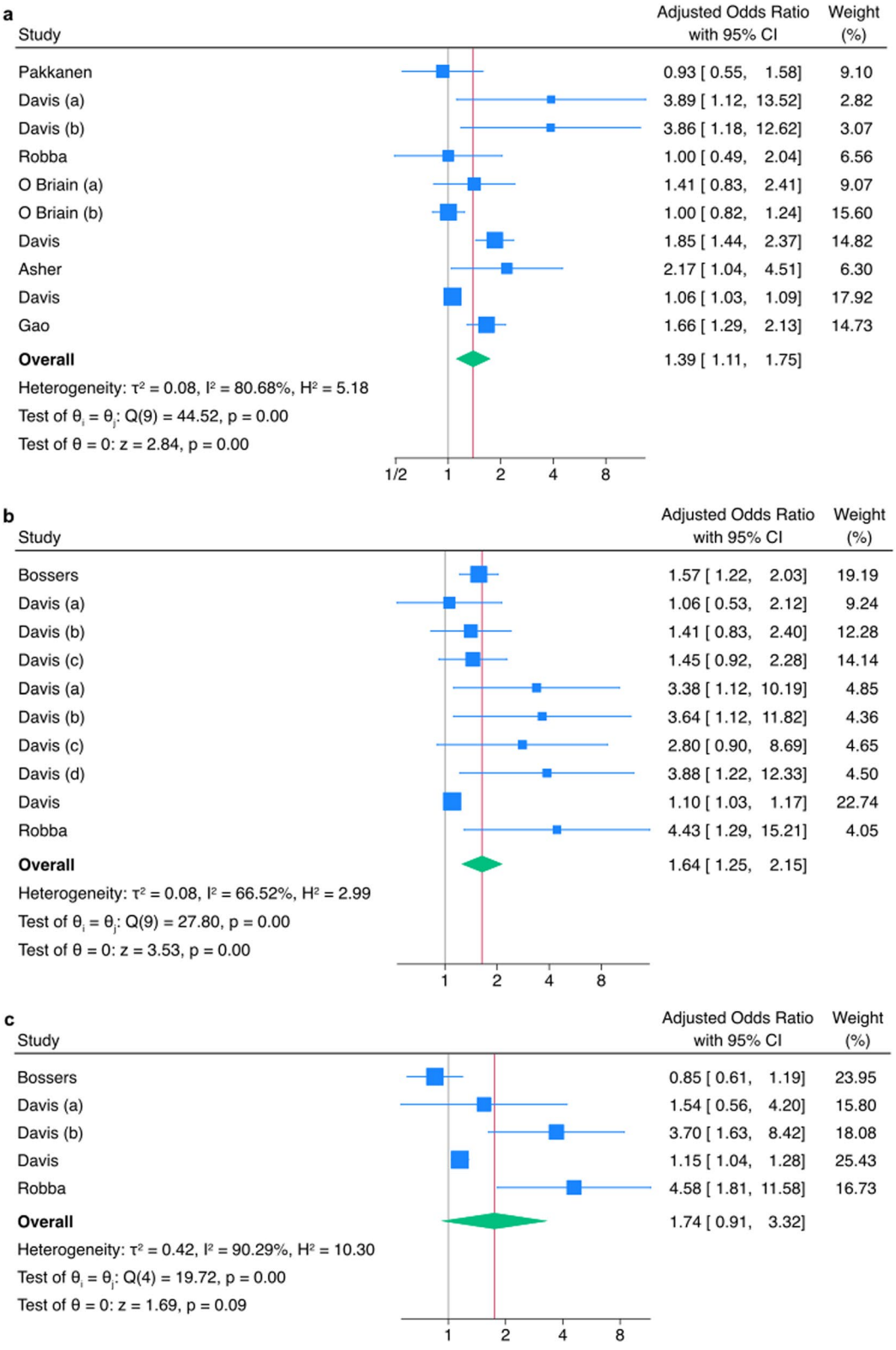

Fig. 3 Forest plots showing random-effects meta-analysis of aORs for **a** hypoxia, **b** hypocapnia, and **c** hypercapnia. Factors adjusted for were dependent on the individual studies, including age, sex, hypotension, mechanism of injury, and ISS. The vertical red line represents the summary measure; the vertical gray line represents the line of no effect; the diamond represents the overall pooled effect estimate of aOR

evidence from Davis et al. [22] revealed that both hypocapnia (PCO_2 < 30 mmHg) and hypercapnia (PCO_2 >50 mmHg) at ED arrival were associated with increased mortality and worsened neurological outcomes. The proposed mechanisms for these associations include cerebral vasoconstriction, compromised cardiac output due to increased intrathoracic pressure, early immunologic activation, and an excitotoxic-inflammatory cascade that may intensify secondary brain injury. Notably, the most rapid rise in detrimental cytokine release and alveolar damage appears to occur within the first 60 to 120 min of ventilation [22]. These findings highlight the potential harms of deviating from normocapnic targets and reinforce the importance of maintaining $PaCO_2$ within a physiologic range during the acute phase.

Howard et al. [36] further expanded on this evidence through a systematic review assessing the impact of ventilation patterns during initial trauma resuscitation on outcomes in patients with TBI of all ages and severities. They concluded that both hyperventilation and hypoventilation during early care were associated with increased mortality and unfavorable neurologic outcomes, particularly in the prehospital and ED settings. Building upon these findings, our meta-analysis provides pooled, quantitative estimates specifically focused on adults with msTBI, reinforcing the detrimental impact of hypocapnia and offering statistically robust associations that complement prior evidence and may strengthen future guideline development.

Despite evidence linking hypocapnia to increased mortality, controlled hyperventilation and permissive hypocapnia remain common in acute neurocritical care [37]. These interventions aim to reduce intracranial pressure (ICP) by inducing cerebral vasoconstriction and lowering cerebral blood volume (CBV). Additionally, hyperventilation may help mitigate lactic acidosis by reducing the intracranial pH [22]. However, these physiological effects may be counterproductive, especially in patients with diffuse cerebral edema, where reduced cerebral blood flow (CBF) can exacerbate ischemic injury. As such, the use of hyperventilation must be carefully balanced, and the potential harms of excessive hypocapnia should be considered in the context of its short-term benefits. These concerns highlight the ongoing need for evidence.

The association between hypercapnia and mortality was weak before and after confounder adjustment. This finding may be the result of a limited number of studies assessing hypercapnia in this population. Only 3 cohorts were included in the unadjusted analysis, and 5 cohorts were included in the adjusted analysis, so the ability to make definitive conclusions about this relationship was limited. This highlights a gap in current research evaluating the effects of hypercapnia in adult TBI patients. In addition to the small sample size, another reason why this association may have been weak was that hypercapnia may have varied effects on clinical outcomes depending on the degree to which it is present. One review reported that mild to moderate hypercapnia ($PaCO_2$ 60-100 mmHg) had a protective effect on TBI patients through cerebral vasodilation, whereas severe hypercapnia exacerbated TBI [38]. The articles included in this study did not investigate the effects of permissive hypercapnia, which highlights the need for future research. Further studies should be conducted to evaluate this concept and determine the specific thresholds at which hypercapnia provides either clinical benefit or increased morbidity and mortality.

Pooled results showed significant associations between hypoxia, hypocapnia, and mortality, but these differences often did not remain significant after subgroup analyses by O_2 or CO_2 parameters. This limits the generalizability of our findings, as the associations were not as robust when accounting for differences in how hypoxia and hypocapnia were measured. This highlights a need for the standardization of physiologic thresholds and consistent methods of measurement. Future clinical trials should evaluate the effects of early hypoxia and hypocapnia at varying thresholds in adults with msTBI to address the identified knowledge gaps and guide the creation of evidence-based treatment protocols.

This review has several strengths. A comprehensive and updated search encompassing 11 databases was performed, identifying articles published from inception until October 23, 2024. This resulted in a large total cohort of over 41,000 patients from several countries, allowing for increased statistical power and more generalizable results. An extensive meta-analysis was also conducted, in which the effect size measures were unified to increase statistical power. Another strength is that language bias in the analysis was eliminated by not restricting the inclusion criteria to only studies published in English. Finally, subgroup analyses by TBI severity and O_2 or CO_2 parameters were performed to determine whether there were potential confounding factors affecting the results.

This study has several limitations. There were moderate to high levels of heterogeneity identified across all exposure-outcome pairs. This was likely caused by differences in sample size, effect size, and demographic characteristics. Some heterogeneity was mitigated by using a random-effects model, performing meta-regression and leave-one-out analyses, converting all effect sizes to the same metric (odds ratios), and the use of subgroup analyses by TBI severity and O_2 or CO_2 parameters. Publication bias was also prevalent, which was intended to be mitigated by conducting a comprehensive literature search encompassing several databases, performing trim-and-fill analyses, and not implementing a minimum

sample size as an inclusion criterion. Most included studies measured secondary brain insults in-hospital, but failed to consistently report specific measurement timing. Secondary injuries such as hypoxia have been more consistently associated with mortality when they present immediately following TBI than when they have a delayed presentation [30]. The findings of this study are limited by the lack of specificity for how soon these insults occurred in-hospital, likely resulting in the pooling of early and late insults together. All studies included in the analysis were observational, which inherently lack randomization and are susceptible to confounding. This study design limits the level of causal inference between these secondary brain insults and mortality. Another limitation is that the hypercapnia analyses included only 3 cohorts in the unadjusted group and 5 cohorts in the adjusted group. The small number of included cohorts ($n < 10$) limits the statistical power for several analyses, including Begg's test, Egger's test, and I^2 [39, 40]. The use of a binary outcome such as mortality without intermediate outcomes such as CT prognostication limits the interpretability of associations. Furthermore, the conversion of other effect size measures, such as the observed-predicted survival difference (OPSD), to OR introduced some uncertainty. Finally, there was an unequal distribution of the articles across WHO regions, with only 3 including study centers located in South-East Asia and zero studies from Africa or the Eastern Mediterranean. Given the potential epidemiological differences in these locations, the generalizability of the results is limited.

Conclusions

This review demonstrated that hypoxia and hypocapnia are associated with increased mortality in msTBI patients. The limited data concerning hypercapnia highlight the need for further research to refine current TBI management guidelines.

Abbreviations

AIS	Abbreviated injury scale
aOR	Adjusted odds ratio
BTF	Brain trauma foundation
CI	Confidence interval
GCS	Glasgow coma scale
GOS-E	Glasgow outcome scale-extended
GRADE	Grading of recommendations assessment, development and evaluation
ICP	Intracranial pressure
ICU	Intensive care unit
MOOSE	Meta-analysis of observational studies in epidemiology
msTBI	Moderate to severe traumatic brain injury
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International prospective register of systematic reviews
RCT	Randomized controlled trial

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05604-3.

Additional file 1. Definitions of TBI, Hypoxia, Hypocapnia, Hypercapnia. Table S1. PRISMA Checklist. Table S2. MOOSE Checklist. Table S3. Database Results Table and MEDLINE Search Strategy. Table S4. Hypoxia Study Characteristics. Table S5. Hypocapnia Study Characteristics. Table S6. Hypercapnia Study Characteristics. Table S7. NOS Analysis. Table S8. GRADE Analysis. Table S9. Heterogeneity. Table S10. Publication Bias. Figure S1. Crude Hypoxia Subgroup Analysis. Figure S2. Adjusted Hypoxia Subgroup Analysis. Figure S3. Crude Hypocapnia Subgroup Analysis. Figure S4. Crude Hypercapnia Subgroup Analysis. Figure S5. Adjusted Hypercapnia Subgroup Analysis. Figure S6. Crude Hypoxia Galbraith Plot. Figure S7. Adjusted Hypoxia Galbraith Plot. Figure S8. Crude Hypocapnia Galbraith Plot. Figure S9. Adjusted Hypocapnia Galbraith Plot. Figure S10. Crude Hypercapnia Galbraith Plot. Figure S11. Adjusted Hypercapnia Galbraith Plot. Figure S12. Adjusted Hypoxia Funnel Plot. Figure S13. Crude Hypocapnia Funnel Plot. Figure S14. Adjusted Hypocapnia Funnel Plot. Figure S15. Adjusted Hypercapnia Funnel Plot

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Author contributions

TAJ, MCSA, AR, AAR, AVL, FAZ, and TC conceptualized the idea. MCSA and AR created the PROSPERO submission. ME designed and executed the database search strategies. TAJ, MCSA, AR, and AAR screened titles, abstracts, and extracted data. TC performed the meta-analysis. TAJ drafted the initial manuscript. ME drafted the search methodology section of the manuscript. All authors reviewed and edited the manuscript prior to submission. All authors had full and equal access to the included data and agreed to have this study be submitted for publication.

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Data availability

All data used in this study is available to be used for future research upon request from the corresponding author, Dr. Tumul Chowdhury (tumul.chowdhury@uhn.ca).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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References

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018;130(4):1080–97.
2. Hong WP, Hong KJ, Shin SD, et al. Association of flow rate of prehospital oxygen administration and clinical outcomes in severe traumatic brain injury. J Clin Med. 2021;10(18): 4097.
3. Ng SY, Lee AYW. Traumatic brain injuries: pathophysiology and potential therapeutic targets. Front Cell Neurosci. 2019;13: 528.
4. Caulfield EV, Dutton RP, Floccare DJ, Stansbury LG, Scalea TM. Prehospital hypocapnia and poor outcome after severe traumatic brain injury. J Trauma. 2009;66(6):1577–83.
5. Bossers SM, Mansvelder F, Loer SA, et al. Association between prehospital end-tidal carbon dioxide levels and mortality in patients with suspected severe traumatic brain injury. Intensive Care Med. 2023;49(5):491–504.
6. Seo DE, Shin SD, Song KJ, Ro YS, Hong KJ, Park JH. Effect of hypoxia on mortality and disability in traumatic brain injury according to shock status: a cross-sectional analysis. Am J Emerg Med. 2019;37(9):1709–15.
7. Shen H, Liu H, He J, Wei L, Wang S. Risk factors of prognosis in older patients with severe brain injury after surgical intervention. Eur J Med Res. 2023;28(1): 479.
8. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury. Fourth Edition Neurosurgery. 2016;80(1):6–15.
9. Zhong H, Feng Y, Shen J, et al. Global burden of traumatic brain injury in 204 countries and territories from 1990 to 2021. Am J Prev Med. 2025;68(4):754–63.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
11. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology. A Proposal Rep JAMA. 2000;283:2008–12.
12. Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000.
13. Balshem H, Helfand M, Schünemann HJ, et al. GRADE: 3. guidelines Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.
14. Lee SW, Hong YS, Han C, et al. Concordance of end-tidal carbon dioxide and arterial carbon dioxide in severe traumatic brain injury. J Trauma. 2009;67(3):526–30.
15. Esnault P, Roubin J, Cardinale M, et al. Spontaneous hyperventilation in severe traumatic brain injury: incidence and association with poor neurological outcome. Neurocrit Care. 2019;30(2):405–13.
16. Vos PE, Jacobs B, Andriessen TM, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology. 2010;75(20):1786–93.
17. Davis DP, Dunford JV, Ochs M, Park K, Hoyt DB. The use of quantitative end-tidal capnometry to avoid inadvertent severe hyperventilation in patients with head injury after paramedic rapid sequence intubation. J Trauma. 2004;56(4):808–14.
18. Pakkanen T, Nurmi J, Huhtala H, Silfvast T. Prehospital on-scene anaesthetist treating severe traumatic brain injury patients is associated with lower mortality and better neurological outcome. Scand J Trauma Resusc Emerg Med. 2019;27(1): 9.
19. O'Connell KM, Littleton-Kearney MT, Bridges E, Bibb SC. Evaluating the joint theater trauma registry as a data source to benchmark casualty care. Mil Med. 2012;177(5):546–52.
20. Robba C, Battaglini D, Abbas A, et al. Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-injured patients: a secondary analysis of the ENIO study. Intensive Care Med. 2024;50(2):234–46.
21. Asher SR, Curry P, Sharma D, et al. Survival advantage and PaO_2 threshold in severe traumatic brain injury. J Neurosurg Anesthesiol. 2013;25(2):168–73.
22. Davis DP, Idris AH, Sise MJ, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury. Crit Care Med. 2006;34(4):1202–8.
23. Davis DP, Meade W, Sise MJ, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009;26(12):2217–23.
24. Davis DP, Peay J, Sise MJ, et al. Prehospital airway and ventilation management: a trauma score and injury severity score-based analysis. J Trauma. 2010;69(2):294–301.
25. Crockard HA, Coppel DL, Morrow WF. Evaluation of hyperventilation in treatment of head injuries. Br Med J. 1973;4(5893):634–40.
26. Para RA, Sarmast AH, Shah MA, et al. Our experience with management and outcome of isolated traumatic brain injury patients admitted in intensive care unit. J Emerg Trauma Shock. 2018;11(4):288–92.
27. Robba C, Battaglini D, Cinotti R, et al. Individualized thresholds of hypoxemia and hyperoxemia and their effect on outcome in acute brain injured patients: a secondary analysis of the ENIO study. Neurocrit Care. 2024;40(2):515–28.
28. Gao G, Wu X, Feng J, et al. Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study. Lancet Neurol. 2020;19(8):670–7.
29. Briain Ó, D, Nickson C, Pilcher DV, Udy AA. Early hyperoxia in patients with traumatic brain injury admitted to intensive care in Australia and new Zealand: a retrospective multicenter cohort study. Neurocrit Care. 2018;29(3):443–51.
30. Davis DP, Dunford JV, Poste JC, et al. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. J Trauma. 2004;57(1):1–10.
31. Lal D, Weiland S, Newton M, Flaten A, Schurr M. Prehospital hyperventilation after brain injury: a prospective analysis of prehospital and early hospital hyperventilation of the brain-injured patient. Prehosp Disaster Med. 2003;18(1):20–3.
32. Chi JH, Knudson MM, Vassar MJ, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. J Trauma. 2006;61(5):1134–41.
33. Yan EB, Satgunaseelan L, Paul E, et al. Post-traumatic hypoxia is associated with prolonged cerebral cytokine production, higher serum biomarker levels, and poor outcome in patients with severe traumatic brain injury. J Neurotrauma. 2014;31(7):618–29.
34. Orr TJ, Lesha E, Kramer AH, et al. Traumatic brain injury: a comprehensive review of biomechanics and molecular pathophysiology. World Neurosurg. 2024;185:74–88.
35. Maiga AW, Lin HS, Wisniewski SR, et al. Adverse prehospital events and outcomes after traumatic brain injury. JAMA Netw Open. 2025;8(1):e2457506.
36. Howard MB, McCollum N, Alberto EC, et al. Association of ventilation during initial trauma resuscitation for traumatic brain injury and post-traumatic outcomes: a systematic review. Prehosp Disaster Med. 2021;36(4):460–5.
37. Bogossian EG, Peluso L, Creteur J, Taccone FS. Hyperventilation in adult TBI patients: how to approach it? Front Neurol. 2021;11: 580859.
38. Deng RM, Liu YC, Li JQ, Xu JG, Chen G. The role of carbon dioxide in acute brain injury. Med Gas Res. 2020;10(2):81–4.

39. Page MJ, Higgins JP, Sterne JA. Assessing risk of bias due to missing results in a synthesis. Cochrane Handbook for Systematic Reviews of Interventions. 2019.
40. von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. BMC Med Res Methodol. 2015;15:35.

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